REMARKS

The February 12, 1999 Official Action has been carefully reviewed. In view of the amendments presented herewith and the following remarks, favorable reconsideration and allowance of this application are respectfully requested.

At the outset, Applicants note that the Examiner has indicated that claims 37, 39, 40 and 44-52 have been allowed.

To conform with the 37 C.F.R. §1.72(b), Applicants submit the required abstract of the disclosure herewith.

At page 2 of the Official Action the Examiner has rejected claims 1,2, 31, and 36 under 35 U.S.C. §112, first paragraph as allegedly containing subject matter which was not described in the specification in such a way as to indicate the inventors were in possession of the claimed invention at the time the application was filed.

Claims 31, 34-35. 38, 41-43 and 53-57 are rejected under 35 U.S.C. §112, second paragraph as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter regarded as the invention.

At Page 4 of the February 12, 1999 Official Action, the Examiner indicates that Claims 3, 30 and 34-35 would be allowable if rewritten in independent form, including all the limitations of the base claim and any intervening claims.

In view of the present claim amendments and the following remarks, Applicants respectfully submit that the claims are in condition for allowance. Accordingly, each of the above-noted objections and rejections under 35 U.S.C. §112, first and second paragraphs are, therefore, respectfully traversed.

REJECTION UNDER 35 U.S.C.§112, FIRST PARAGRAPH

The Examiner has rejected claims 1, 2, 31-33 and 36 under 35 U.S.C. §112, first paragraph as allegedly failing to be commensurate in scope with the present specification. It the

Examiner's position that Applicants have not disclosed any other expression vectors, procedures for generating such vectors or any correlation between the function and structure of the claimed vectors.

The Examiner's attention is drawn to newly presented claims 58-60. The present invention relates to a system that allows expression of a desired gene to be associated with the expression of a selectable marker. In this way, cells having optimal expression levels of the gene of interest can be identified. More specifically, the claimed invention is based on a recombinant nucleic acid construct comprising the gene of interest operably linked to a selectable marker gene such that selectable marker protein expression occurs as a result of translation reinitiation. While recombinant retroviral vectors are exemplified herein, it is clear that the constructs of the invention may also be inserted into conventional plasmid vectors. Such recombinant techniques are well known to those of ordinary skill in the art and are clearly enabled by the disclosure in the present application.

In the February 12, 1999 Official Action the Examiner acknowledges that the invention as it relates to retroviral vectors is fully enabled by the description. In light of that acknowledgement, the statement that the applicants were not in possession of the claimed invention at the time of filing is not understood. Applicants have clearly described and fully enabled an important embodiment of the present invention.

The need for fair protection governs both the considerations concerning the scope of claims and the requirements for sufficient disclosure. For example, unless the claims also contain variants of components, which were at the time or later on, equally suited to achieving the same effect in a manner which could not have been envisaged without the invention, the protection provided by the patent would be

ineffectual. Therefore, an invention is sufficiently disclosed if at least one way is clearly enables the skilled person to carry out the invention. That being said, the protection conferred by a patent should correspond to the technical contribution to the art made by the disclosure of the invention described therein, which excludes the patent monopoly being extended to subject-matter which after reading the patent specification and considering common general knowledge, would still not be at the disposal of the skilled person.

It is submitted, for the following reasons, that the skilled person is able to achieve the envisaged result within the whole ambit of the claim without undue difficulty, and that the description with or without the relevant common general knowledge provides a fully self-sufficient technical concept as to how this result is to be achieved.

To be enabling under 35 U.S.C. § 112, a patent must contain a written description that enables one skilled in the art to make and use the claimed invention without undue experimentation. Atlas Powder Co. v E.I. Du Pont De Nemours & Co., 224 USPQ 409, 413 (CAFC1984). "An inventor need not, however, explain every detail since he is speaking to those skilled in the art" DeGeorge v. Bernier, 226 USPQ 758. Therefore, with regard to the written description requirement, Applicants wish to point out that it is well settled case law that the claimed subject matter need not be set forth "literally or *in haec verba*" in order for the specification to satisfy the written description requirement of 35 U.S.C. § 112, first paragraph (in re Lukach, 169 USPQ 795). All that is required for an adequate written description is that the specification "convey clearly to those skilled in the art, to whom it is addressed, in any way, the information that the applicant has invented the specific subject matter later

claimed" (In re Wertheim, 191 USPQ 90, 97).

The present invention lies in the realisation that, although re-initiation of translation is a relatively inefficient process, it can be used in a system for determining optimal expression levels. The crux of the invention thus lies in the idea of positioning a selectable marker in the vicinity of the desired gene within an expression vector, to ensure that translation re-initiation is required before the selectable marker protein is expressed. By detecting the expression levels of the selectable marker, the hosts providing optimal expression levels of the desired genes can be determined.

This inventive concept is applicable to a number of standard molecular biological systems or techniques used commonly in the laboratory. Therefore, to ensure that the applicants get fair and just protection for their invention, it is important that the scope of the claims reflect their contribution to the art.

As mentioned previously, the specification primarily describes use of the invention in retroviral vectors and retroviral packaging cell lines. However, as is apparent from reading the specification, the inventive concept is applicable to all known types of vectors, e.g. expression plasmids or viral vectors (see page 3 lines 1-3 of the specification). The inventors have described and provided comprehensive working examples of a particular embodiment of the invention (as acknowledged by the examiner). However, the examiner is of the opinion that the skilled person to whom the application is addressed, would be faced with undue experimental burden in applying the invention to vectors other than retroviral systems.

Taking each of the examiner's objections in turn:

1) **No disclosure of other expression vectors.**

The term vector is commonly used in the art to include phage, plasmid or virus nucleic acid into which another nucleic acid sequence may be inserted for introduction into bacterial or other cells for amplification or studies of gene expression.

Claim 1 of the present invention refers to expression vectors. These vectors allow genes within a cloned insert to be expressed by transcription from a strong promoter in the vector. For example using SV40 vectors, a desired product may be expressed efficiently in eukaryotic cells. These systems are extremely well known to those skilled in the art and a regular tool in the field of molecular biology (see for example, Chapter 16 of Molecular Cloning - A Laboratory Manual 2nd edition, Sambrook, Fritsch and Maniatis).

2) **No disclosure of any procedures for generating said vectors**

The specification describes in detail the preparation of plasmids. See pages 18 to 20. For example, the production of a plasmid (FBASAF) comprising a gene of interest (env gene) and a selectable marker (phleo selection marker) is described. The example describes the use of PCR primers to amplify the gene of interest and insert a restriction site into the sequence immediately after the env stop codon. It then describes co-ligation of the fragments into the plasmid so that the phleo selectable marker was expressed from the same mRNA as the env gene. As this is an example, specific PCR primers and DNA fragments are used. However, the teaching of this example can be easily generalised to apply to other fragments and plasmids.

Expression of proteins from cloned genes is common general knowledge to the addressee of the present application (see for example, Chapter 16 of Molecular Cloning - A

Laboratory Manual 2nd edition, Sambrook, Fritsch and Maniatis).

3) **No disclosure of cell lines for packaging or producing said vectors**

The examiner is of the opinion that the present specification is lacking adequate disclosure of cell lines for packaging or producing vectors. This objection is not understood. As mentioned above, the invention relates to an expression system that allows detection of cells expressing a desired gene at optimum levels. This system uses a selectable marker in order to carry out this detection. As described in the specification, the selectable marker may be a protein that can be detected via its phenotype or via its function (see page 3 lines 5 to 10). Therefore, knowledge of cell lines for packaging vectors is not essential to the present invention. However, that being said, such cell lines are commonly used in the field of molecular biology and would not present the skilled person with any difficulty should he wish to utilise the invention in this way. Any cell line that is capable of being grown in culture and which allows DNA and a selectable marker to be introduced into it will satisfy the requirements of the invention. Exemplary cell lines include HeLa cells, COS cells or CHO cells. Again, such cells are described in Chapter 16 of Molecular Cloning - A Laboratory Manual 2nd edition, Sambrook, Fritsch and Maniatis. Indeed methods for introducing the DNA constructs of the invention into such cell types are well known to those of ordinary skill in the art. In light of the foregoing, Applicants respectfully submit that the claims as presently amended are enabled by the disclosure in the specfication. Accordingly, Applicants respectfully request that the rejection of claims 1, 2, 31-33 and 36 be withdrawn.

REJECTION UNDER 35 U.S.C. §112, SECOND PARAGRAPH

The Examiner has rejected claims 31, 34, 35, 38, 41-43 and 53-57 as indefinite for allegedly failing to particularly point out and distinctly claim the subject matter regarded as the invention.

Specifically, the Examiner finds claim 31 vague for the recitation of a "gene of interest is included as part of a viral packaging construct" Applicant respectfully submits that the expression vector of claim 1 does not require that the gene of interest be expressed as part of a viral packaging construct. As set forth above, Applicant contemplates the use of the nucleic acid constructs of the invention in conventional plasmid systems. Such systems would not involve the use of viral packaging constructs. Retroviral packaging constructs are utilized to provide in trans the retroviral proteins encoded by the gag, pol and env genes. If the construct of the invention is utilized in a recombinant retroviral vector expression system, operably linking the DNA construct of the invention to a viral packaging construct facilitates the practice of the present invention. Applicant submits that claim 31 is properly dependent and provides a limitation on the subject matter claimed in claim 1 and accordingly requests that the rejection of claim 31 be withdrawn.

The Examiner finds claim 34 vague for failing to recite the production of a cell line in which a gene of interest is expressed in accordance with the preamble. The claim has been amended to include this recitation.

Claim 38 is allegedly vague for the recitation "according to claim 37 being human complement-resistant". The claim has been amended to incorporate the Examiner's helpful suggestion, thereby rendering this claim rejection moot.

Claim 41 is vague for the lack of antecedent basis for

the term "the packaging deficient construct comprising the viral env gene and the second selecable marker". The claim has been amended to substitute the word "the" with --a--, thereby rectifying the alleged vagueness of the claim.

Claim 42 is allegedly vague for the recitation of "the recombinant expression vector from claim 37" as claim 37 recites two recombinant expression vectors. Claim 42 has been amended to recite that the first recombinant expression vector is a packaging deficient retroviral helper construct. New claim 61 has been added and is directed to the second recombinant expression vector of claim 37 being a packaging deficient retroviral helper construct. These amendments serve to clarify the meaning of the claim.

It is the Examiner's position that claim 43 is vague for lacking proper antecedent basis for the recitations "the retroviral vector" and "the packaging deficient genome". The claims have been amended to recite "a" retroviral vector and "a" packaging deficient genome, thereby removing this ground of rejection.

Claims 53 and 54 are allegedly vague for the recitation of "packaging cells comprises human HT1080 cells" and "packaging cells comprises human TE671 cells and express RD114 envelopes" as it is unclear how a cell can comprise a cell. The claims have been amended to incorporate the helpful suggestion of the Examiner. Claim 54 has been amended to depend from claim 39.

Finally, claim 55 is indefinite for failing to reciting the generation of a retroviral packaging cell in which a gene of interest is expressed. The claim has been amended to provide this step.

The foregoing claim amendments should serve to eliminate any indefinite language. Accordingly, Applicants respectfully request that the rejection of claims 31, 34, 35, 38, 41-43 and

53-57 under 35 U.S.C. §112, second paragraph be withdrawn.

In view of the amendments presented herewith and the foregoing remarks, it is respectfully urged that the rejections set forth in the February 12, 1999 Official Action be withdrawn, and that this application be passed to issue and such action is earnestly solicited.

Respectfully submitted,

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